Remarks

Introduction

The above-identified application has been carefully reviewed in light of the Office Action mailed August 29, 2005, which included a final rejection of the pending claims. Applicant submits that the amendments to the claims and remarks included herein show the present claims to be allowable and do not raise new issues and do not require additional searching. Therefore, applicant respectfully requests that this response be entered and that the rejections of the claims be reconsidered and withdrawn.

Claims 1-9, 17-25, and 28-33 were pending. By way of this response, claims 1, 17, and 30-31 have been amended, and claims 2-7, 18-23, and 32-33 have been cancelled without prejudice. Claims 1, 17, and 30 have been amended to include subject matter from previous claims 2, 5, 18, and 21. For example, each of the present claims recites specific combinations of botulinum neurotoxins (that is a combination of botulinum toxin type A and type B, or a combination of botulinum toxin type A and type E) that are present in a single composition or are administered simultaneously to a patient. Thus, the amendments to the claims are supported by the specification as originally filed, and do not raise new issues. Accordingly, claims 1, 8-9, 17, 24-25, and 28-31 remain pending.

Rejections Under 35 U.S.C. § 103

Claims 1-9, 17-25, and 28-33 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ludlow et al. in view of Simpson (1991) and further in view of Jankovic et al (1991).

The Office Action maintains the Examiner's previous position and indicates that it would have been obvious to a person of ordinary skill in the art to administer botulinum toxin type F in combination with botulinum toxin type A because the patients had developed antibodies to toxin A (emphasis added; Office Action, page 4, first paragraph and page 6, first paragraph). The Office Action also indicates that it would have been obvious to a person of ordinary skill in the art to extend the teachings of Ludlow to serotypes other than type F, and to administer the other serotypes after A as claimed with a reasonable expectation of success (emphasis added; Office Action, page 4, first paragraph and page 6, first paragraph).

Applicant has amended the claims as set forth above, and applicant traverses the rejections as it relates to the present claims.

As a preliminary matter, applicant vigorously disagrees that there is nothing on the record to show that the combination of teachings would not suggest the claimed invention, as suggested by the Examiner.

At least in applicant's paper filed in response to the January 15, 2004 Office Action, applicant submitted evidence supporting the unobviousness of the present invention. In particular, applicant submitted a Declaration of Dr. Mitchell Brin, an expert in the therapeutic use of botulinum neurotoxins. This Declaration is referred to as the Brin Declaration.

The Brin Declaration is evidence indicating that therapeutically using two or more types of botulinum toxin together at the time of the present invention would have been foolhardy and dangerous. In other words, an expert in the therapeutic use of botulinum neurotoxins, who is intimately familiar with the state of the art, states that the use of a

botulinum toxin other than type A, such as a botulinum toxin type B, would be foolhardy and dangerous. The Brin Declaration is clear and substantial evidence demonstrating that a person of ordinary skill in the art would not be motivated to combine two or more different types of botulinum neurotoxins to treat a patient by simultaneous administration of the two or more different types.

As explained in that response, decisions from the courts, which review Patent Office decisions, are instructive as to the deference and weight to be accorded the evidence presented in the Brin Declaration. An expert opinion expressed in a Declaration can overcome an obviousness rejection.

Thus, applicant submits that the record for the above-identified application includes evidence clearly showing that the prior art, including the combination of Ludlow, Simpson, and Jankovic, would not suggest the present invention. At least in view of this evidence, applicant submits that the present claims are unobvious over the prior art and are in condition for allowance.

In addition, applicant provides the following additional remarks to explain why the prior art does not anticipate or make obvious the present claims.

Claim 1 is directed to a method that comprises a step of administering simultaneously to a patient a therapeutically effective amount of a combination of at least two specific types neurotoxins (e.g., a combination which includes botulinum toxin type A and type B, or a combination which includes botulinum toxin type A and type E). Claim 17 is directed to a composition (e.g., one composition) that comprises a therapeutically effective amount of a combination of at least two specific types of neurotoxins (e.g., a combination which includes botulinum

toxin type A and type B, or a combination which includes botulinum toxin type A and type E). Claim 28 is directed to a therapeutic composition (e.g., one composition) that comprises botulinum toxin types A and B. Claim 29 is directed to a therapeutic composition (e.g., one composition) that comprises botulinum toxin types A and E. Claim 30 is directed to a therapeutic composition (e.g., one composition) that comprises at least two different types of botulinum toxin (e.g., a botulinum toxin type A and botulinum toxin types B or E).

In short, the present claims are directed to methods that comprise simultaneously administering at least two specific types of botulinum toxin, and single compositions that comprise two or more specific types of botulinum toxin. In other words, the present claims are directed to subject matter that is different and distinct from methods which comprise administering non-type A serotypes of botulinum toxin after type A toxin has been administered to a patient, as stated in the Office Action.

As indicated previously, Ludlow et al. discloses treatment of torticollis by administering botulinum toxin type F to patients who have antibodies to botulinum toxin type A. Ludlow discloses a composition which comprises only one type of botulinum toxin, i.e., botulinum toxin type F. Ludlow discloses a method of treating a patient by administering botulinum toxin type F to a patient at a different time (i.e., not simultaneously) than botulinum toxin type A, for example, botulinum toxin type F is administered to the patients after the patients received botulinum toxin type A therapy.

Simpson is a review article describing various features of botulinum toxin, including distinct antigenicities among the various serotypes and similar properties of inhibiting acetylcholine release. Although Simpson discloses that the

different serotypes share a common feature of inhibiting acetylcholine release, Simpson also discloses that the mechanisms of action vary among the different serotypes.

Jankovic is a review article discussing therapeutic uses of botulinum toxin type A. Jankovic discloses that patients with antibodies against botulinum toxin type A will likely respond to injections with other botulinum toxins that are immunologically distinct from botulinum toxin type A.

Applicant submits that the combination of Ludlow, Simpson, and Jankovic does not disclose, teach, or suggest the present invention. For example, the combination of Ludlow, Simpson, and Jankovic does not disclose, teach, or even suggest a method which comprises simultaneous administration (e.g., at the same time, not at different times), or a single composition that comprises at least two specific different types of botulinum toxin (i.e., a combination of botulinum toxin type A and type B, or a combination of botulinum toxin type A and type E).

Applicant disagrees that the references have been argued individually as opposed to the combination. Applicant has repeatedly identified what each of the references has disclosed individually, and in combination. Furthermore, applicant has explained how the combination of references fails to disclose, teach, or even suggest all of the elements recited in the present claims (i.e., simultaneous administration of two or more different types of botulinum neurotoxins and single compositions containing two or more different types of botulinum neurotoxins). Simply put, the combination of references only discloses separate administration of different types of botulinum neurotoxins (i.e., not simultaneous administration) or separate compositions each containing a single type of botulinum

neurotoxin (i.e., not a single composition comprising a combination of two or more botulinum neurotoxins).

Applicant acknowledges that the combined teachings of the references make up the state of the art. However, the combined teachings fail to disclose, teach, or even suggest the use of two or more neurotoxins at the same time, either by simultaneous administration, as recited in claim 1, or in a single composition, as recited in claims 17, 28, 29, and 30. Thus, applicant maintains that the prior art fails to disclose, teach, or even suggest the present invention.

Applicant resubmits that the Office Action acknowledges the deficient teachings of the combination of references. In particular, the Office Action specifically states that it would be obvious to administer a non-type A serotype of botulinum toxin after separate administration of botulinum toxin type A.

In clear and direct contrast to the teachings of the prior art, and the remarks in the Office Action, the present claims are directed to a method which comprises simultaneously administering at least two different types of botulinum toxin (i.e., types A and B or types A and E). In other words, the second botulinum toxin is not administered after the type A botulinum toxin is administered. In direct contrast, the prior art only teaches the sequential (i.e., not simultaneous) administration of a single type of botulinum toxin (type F) after administration of a botulinum toxin type A and the development of antibodies to type A botulinum toxin. The prior art does not disclose, teach, or even suggest administration of two or more botulinum toxins at the same time or simultaneously, as recited in the present claims.

Thus, applicant submits that the combination of Ludlow et al., Simpson, and Jankovic does not disclose, teach, or even

suggest all of the elements recited in the present claims, and in claims 1, 8, and 9 in particular.

In addition, applicant submits that the general disclosure by Simpson of the different serotypes of botulinum toxin does not provide any motivation or incentive to a person of ordinary skill in the art to combine Ludlow et al., Simpson, and Jankovic for any purpose, let alone to combine Ludlow et al., Simpson, and Jankovic and specifically provide at least two different botulinum toxin types (i.e., botulinum toxin types A and B, or botulinum toxin types A and E) in a single composition, as recited in claims 17, 24-25, and 28-31.

In specific reference to the present claims, applicant maintains and re-submits that, based on the teachings of Ludlow et al., Simpson, and Jankovic, alone or in any combination, a person of ordinary skill in the art would still be required to guess, test, speculate, and/or arbitrarily "pick and choose" two specific neurotoxins (e.g., botulinum toxin types A and B or A and E) from among the list of seven different botulinum toxins identified by Simpson, as recited in claims 17, 28, 29, and 30. Simpson does not place any significance whatsoever in the types of botulinum toxin, let alone in a combination of botulinum toxin types A and B, or A and E, relative to the other botulinum toxins disclosed.

This lack of significance or suggestion is supported in the Office Action by the Examiner's apparent opinion that a person of ordinary skill in the art would be motivated to use <u>any</u> combination of botulinum toxin serotypes. Although the Office Action indicates that "any" combination may be obvious, the Office Action fails to indicate where the combination of references specifically discloses, teaches, or suggests the specific combinations of botulinum neurotoxins recited in the

present claims (i.e., botulinum toxin types A and B or botulinum toxin types A and E).

Simply put, the general disclosure in Simpson of botulinum toxin A through G is insufficient for Simpson, alone or in any combination with Ludlow et al. and Jankovic, to teach or suggest the method recited in claim 1, and the compositions recited in claims 17, 28, 29, and 30. For example, the general disclosure of botulinum toxin types A through G is insufficient for Simpson, alone, or in combination with Ludlow et al. and Jankovic, to teach or suggest a therapeutic composition comprising botulinum toxin types A and B or botulinum toxin types A and E, as recited in the present claims.

Only after knowing of applicant's invention and disclosure would one of ordinary skill in the art select and combine two or more different types of botulinum toxin, such as types A and B, or A and E, in a single composition from among the seven different botulinum toxins disclosed by Simpson. Applicant submits that such hindsight is an improper basis for rejecting patent claims.

In addition, applicant submits that the prior art does not disclose, teach, or even suggest the composition of claim 30, wherein the amount of the first neurotoxin is greater than the amount of the second neurotoxin, as recited in claim 31. As discussed above, applicant submits that the prior art does not disclose, teach, or even suggest a single composition comprising two or more different botulinum neurotoxins, let alone, disclose, teach, or suggest the specific types and amounts of the botulinum neurotoxins, as recited in claims 30 and 31.

Therefore, applicant submits that the record includes substantial evidence rebutting the obviousness of the present claims, that the prior art fails to disclose, teach, or suggest

all of the elements recited in the present claims (e.g., a combination of two or more botulinum neurotoxins being simultaneously administered or provided in a single composition), and that the prior art fails to disclose, teach, or even suggest the specific combinations of types of botulinum toxins recited in the present claims (i.e., a combination of botulinum toxin types A and B, or a combination of botulinum toxin types A and E).

In view of the above, applicant submits that the present claims, and claims 1, 8, 9, 17, 24, 25, and 28-31 in particular, are unobvious from and patentable over Ludlow et al., Simpson, and Jankovic, alone or in any combination, under 35 U.S.C. § 103.

Each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present methods and compositions including the additional feature or features recited in any of the present dependent claims, such as the specific combinations of neurotoxins. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

Conclusion

In conclusion, applicant has shown that the present claims are unobvious from and patentable over the prior art under 35 U.S.C. § 103. Therefore, applicant submits that the present claims, that is claims 1, 8, 9, 17, 24, 25, and 28-31 are allowable. Therefore, applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the

Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: 10/31/05

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